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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Davis Wright Tremaine LLP
Barry L Davison
2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 11/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,243	MARKL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 11, 2002. Currently, claims 1-4, 7-12 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection necessitated by amendment.

New Grounds of Rejection Necessitated by Amendment

New Matter

4. Claims 1-4, 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "at least 98% identical to SEQ ID NO: 34-38" are included. The specification does not describe or discuses "at least 98% identical to SEQ ID NO: 34-38". Instead the specification describes a nucleotides sequence of at least 98% identical to SEQ ID NO: 34-38. The specification does not clearly provide basis for the limitation of "at least 98% identical to SEQ ID NO: 34-38." It appears that the response may be relying upon the fact that there are 22 variable nucleotide position out of 1,248 listed nucleotides positions to arrive at 2% variation (page 6 of response filed September 11, 2002). However, SEQ ID NO: 34, contains 5 positions within SEQ ID NO: 34 contain an "n". This does not support further sequence variability in addition

to the already present 0.013 variability. Moreover, SEQ ID NO: 35 contains 2 variable positions within the 213 base pair nucleic acid. This is less than 1% variability. SEQ ID NO: 37 contains one variable nucleotide in the 369 base pair sequence. The specification does not appear to have contemplated nucleotide sequence aside from nucleotide sequences greater than 90%. Therefore, "at least 98% identical to SEQ ID NO: 34-38" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

5. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 appears to contain all the limitations of Claim 7.

Maintained Rejections

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to DNA sequences and methods using DNA sequences having at least 90% identity with SEQ ID NO: 34-38, CpG island sequences associated with SEQ ID NO: 34-38, CpG island sequences associated with sequence having a nucleotide sequence at least 90% identical to SEQ I DNO: 34-38 and combinations thereof.

The specification describes sequencing 103 "novel" sequences. The specification fails to teach the chromosomal location, the gene, or the cDNA of these DNA sequence fragments.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its ennablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of specifies have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Similar to Example 7 of the Written Description guidelines, the specification teaches a fragment of a cDNA or genomic DNA, but does not provide the full cDNA or genomic DNA.

The specification does not appear to have described any sequences which are 90% identical with SEQ ID NO: 34-38 and have the same asserted function for detecting cancer.

The specification has not provided any description of sequences "associated with SEQ ID NO: 34-38". The specification does not appear to define what "associated" means in a clear and definite way. It is unclear whether "associated" means that the "associated" nucleic acid sequence contains similar nucleotides, is located adjacent to SEQ ID NO: 34-38 on the chromosome, is located on another chromosome, but is involved in the same metabolic pathway or rather associated has a distinct meaning.

Therefore, applicants have not described a representative number of these embodiments within the scope of the claim.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been adequately described. In responding to the examiner's rejection, applicant's have set forth several reasons for traversal which will be addressed in the order argued.

First, the response asserts "independent Claim 1, as originally filed, already recites "consisting of sequences," rather than open-ended comprising language. This argument has been reviewed but is not convincing because while one of the members of the Markush group is directed to SEQ ID NO: 34-38, the other members are directed to "sequences having a nucleotide sequence at least 98% identical to sequences of SEQ ID NO: 34-38". Having is open claim language, much like comprising. Similarly, since "associated with sequences" are not described, the limitation of a size of these sequences has not been provided.

Second, with respect to "associated" CpG island sequences, the response asserts that the specification clearly defines the term. The specification teaches that the CpG island sequence associated with the sequence of a particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence and satisfies the criteria of having both a frequency of CpG diunucleotides corresponding to an Observed/Expected Ration >0.6, and a GC content >0.5 (page 3, lines 24-28). This argument has been reviewed but is not convincing because the specification has not provided a representative number of

associated sequences. The specification has not provided any structure to the "associated sequences." The claims require that only one of nucleotide of the partical SEQ ID NO: is present. The specification has not described a larger portion of a CpG island. Therefore, detecting an associated sequence has not been described. With respect to the arguments directed to the conceptual "association," this concept does not provide support for possession of associated sequences. Conception of an idea does not provide for possession of the product.

Third, the response asserts that sequences with less than 100% have diagnostic utility. This argument has been reviewed but is not convincing because the specification has only provided analysis for a single sequence, namely SEQ ID NO: 34, for example, which contains 5 positions within SEQ ID NO: 34 contain an "n". This does not support further sequence variability in addition to the already present 0.013 variability. Moreover, SEQ ID NO: 35 contains 2 variable positions within the 213 base pair nucleic acid. This is less than 1% variability. SEQ ID NO: 37 contains one variable nucleotide in the 369 base pair sequence. The disclosure does not support a nucleic acid sequence having 98% identity with a sequence which is already variable. The specification has not described such a genus.

Moreover the claims have been amended to include a primer or probe which hybridizes to any region of at least 12 nucleotides of a sequence selected from SEQ ID NO: 34-38 or a sequence having a nucleotide sequence at least 98% identical to SEQ ID NO: 34-38. The specification has not described nucleic acids which hybridize to any 12 nucleotides.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of diagnosis or prognosis of cancer by performing a methlyation assay to determine a diagnosis.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-

altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6).

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5552,277; 5,846,712; 5,856,094).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification clearly teaches that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The instant specification does not appear to have performed any more experimentation than

the mere determination that a basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal. Therefore, the specification appears to be indicating that this is inadequate to allow for effective diagnostic, prognostic or therapeutic application of this knowledge. In essence, it appears as though the specification teaches that the instant invention is not enabled for use in diagnostic, prognostic or therapeutic applications. In order to use this information, the skilled artisan would be required to sample a population of individuals and assess whether each SEQ ID NO: 34-38 is associated differentially expressed in cancer. This experimentation would be trial and error experimentation which would not have predictable results for the reasons provided in the specification, namely "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). In the event that detection of cancer, is not enabled, it is unclear how the polynucleotides may be used.

Second, the specification teaches that SEQ ID NO: 34-38 are hypermethylated as opposed to hypomethylated. The claims appear to be directed to determining that the sequence is aberrantly methylated as indication of cancer. However, it is unpredictable that SEQ ID NO: 34-38 are hypomethylated and in the event that SEQ ID NO: 34-38 are hypomethylated that this is indicative of cancer.

Third, the specification teaches SEQ ID NO: 34-38 were found to be hypermethylated in a prostate cancer tissue sample. The indication that one prostate cancer sample indicated a hypermethylation of the region is not indicative that any and all cancers have the same methylation regions. For example, the bladder cancer samples exemplified in the specification do not appear to have hypermethylation of SEQ ID NO: 34-38. Therefore, it is unpredictable whether hypermethylation of SEQ ID NO: 34-38 is a general marker for all cancers, or whether there is a smaller class of cancers which SEQ ID NO: 34-38 are markers, or finally whether the sequence may only be expressed in prostate cancer.

Finally, the specification has not taught that a predictable correlation exists between nucleic acids which are "associated with SEQ ID NO: 34-38". The specification has not described any associated nucleic acids, therefore, it is unpredictable that "associated DNA sequences" are indicative of cancers absent unpredictable and undue experimentation. The skilled artisan would first be required to determine associated sequences of SEQ ID NO: 34-38 and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer.

Therefore, based upon the unpredictability and the undue experimentation which would be required to be performed prior to practicing the full scope of the method, the instant specification has not enabled the instant claims.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been adequately described. In responding to the examiner's rejection, applicant's have set forth several reasons for traversal which will be addressed in the order argued.

First, the response asserts that the examiner has "inappropriately misconstrued applicant's quoted statements." The response argues that the background section of the specification was intended to mean "to indicated that methylation analyses and correlations need to be made with specific sequences or genes." The specification states "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge." The response asserts that specific sequences are provided in the specification and correlated these markers with cancer, namely bladder and prostate. This argument has been reviewed, but not persuasive because the specification has not identified a correlation between SEQ ID NO: 34-38 and bladder cancer. The examiner has not required any "causative showing", but was illustrating that the specification itself requires actual correlation to enable the invention. Moreover, the specification appear to have only analyzed a single sample. The specification appears to indicate that this is not sufficient, but rather requires more. The specification does not appear to have provided an analysis of more than one sample to illustrate that the nucleic acid is predictably hypermethylated in prostate cancer.

With respect to the third point, the response asserts that the claims have been amended to recite bladder or prostate cancer. The specification has provided no information regarding SEQ ID NO: 34-38 with bladder cancer. Therefore, as provided above, it is unpredictable whether an association exists absent further undue experimentation.

Finally, the response traverses the rejection with respect to the associated sequences within the scope of the claims. With respect to "associated" CpG island sequences, the response asserts that the specification clearly defines the term. The specification teaches that the CpG island sequence associated with the sequence of a particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence and satisfies the criteria of having both a frequency of CpG diunucleotides corresponding to an Observed/Expected Ration >0.6, and a GC content >0.5 (page 3, lines 24-28). This argument has been reviewed but is not convincing because the specification has not provided a representative number of associated sequences. The specification has not provided any structure or assocation with bladder and prostate cancer to the "associated sequences." The specification has not provided a larger portion of a CpG island. Therefore, detecting an associated sequence has not been taught in the specification. With respect to the arguments directed to the conceptual "association," this concept does not provide support for enablement of associated sequences. Conception of an idea does not provide for enablement of the product.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Herman et al. (US Pat. 5,786,146, July 28, 1998).

Herman teaches a kit comprising a reagent which modifies unmethylated cytosine and primers for amplification of the CpG –containing nucleic acid (Claim 15)(limitations of Claim 7). Herman teaches a kit comprising SEQ ID NO: 46 which contains "CTAAAAAT" which is embedded within SEQ ID NO: 34 of the instant application. Therefore, this primer, SEQ ID NO: 36 of Herman, would hybridizes to any region of SEQ ID NO: 34-38, namely region of SEQ ID NO: 34, nucleotides 212-219 (8 nucleotides). This primer comprises at least about 12 nucleotides which are at least 90% identical to SEQ ID NO: 34. Alternatively, the primer comprises 10 nucleotides which are 90% identical to SEQ ID NO: 34. The kit contains bisulfite, amplification buffer which is used in COBRA, Ms-SnuPE, MSP, etc. analysis.

Response to Arguments

The response traverses the rejection. The response asserts that the claim has been amended to require at least 12 nucleotides of a sequence selected from SEQ ID NO: 34-38 or a sequence at least 98% identical with SEQ ID NO: 34-38. This argument has been reviewed but is not convincing because the claim is directed to a probe/primer which Herman teaches would hybridize to any region of at least 12 nucleotides having a nucleotide sequence at least 98% identical to SEQ ID NO: 34. The claim does not require that the primer contains 12 consecutive nucleotides from SEQ ID NO: 34, but rather that the primer hybridizes to a region of 12 nucleotides. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. No claims allowable.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday 7:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 19, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600